REMARKS

Claims 1-34 are pending. Claims 1-15 and 23-27 have been amended to more clearly set forth aspects of the invention. Claims 16-22 and 28-34 are canceled herein without prejudice. Accordingly, amended claims 1-15 and 23-27 and new claims 35-38 are under consideration.

Support for the amendments to the claims is found throughout the specification and in the original claims. Specifically, support for amendment to claim 1 is presented in original claim 1 and at page 7, lines 9-22, wherein support for a solid surface being a graft or biomedical device is found; and at page 12, line 36 through to page 13, line 11, wherein support for seeding a first population of altered endothelial cells having increased cell-to-cell cohesivity is found. Support for amendment to claims 2, 4-6, and 10 is found at page 7, lines 9-22, wherein a graft or biomedical device is described as having a solid surface of the invention. Support for amendment to claim 23 is found at page 7, lines 9-22, wherein applications for the methods of the invention that relate to a graft or biomedical device are described. Support for amendment to claim 24 is found in original claims 24 and 4. Support for amendment to claim 27 is found in original claim 27 and at page 4, lines 8-11, wherein functional molecules are described as those capable of bridging cadherins to the cytoskeleton. Claims 2-7, 10-12, 14-15, and 24-27 are amended to clearly indicate the claims from which these claims depend. Claims 7-9, 11-15, 25, and 27 are amended herein to include commas before the word "wherein" as recited. No issue of new matter is introduced by the amendments to the claims.

Support for new claims 35-38 is found throughout the specification and in the original claims. Specifically, support for amendment to claim 35 is presented in original claim 20 and at page 7, lines 9-12, wherein solid surfaces such as grafts or biomedical devices that are in contact with an arterial and/or venous system are described. Support for new claim 36 is presented at page 1, lines 20-21; at page 2, lines 23-25; and at page 7, lines 9-10 and 19-20, wherein various grafts of the invention are described. Support for new claim 37 is found at page 8, lines 11-12 and Figure 1, wherein vascular grafts are shown and described. Support for new claim 38 is presented at page 7, lines 9-10,

wherein support for tubular grafts is found. No issue of new matter is introduced by the amendments to the claims.

Brief Summary of the Invention

As described in detail in the specification, the present inventors have discovered that human endothelial cells exhibit reduced intercellular cohesitivity as compared to endothelial cells isolated from other mammalian species. This property of human endothelial cells leads to adverse consequences with respect to endothelialization of grafts or biomedical devices (i.e., populating the surfaces of grafts or biomedical devices with endothelial cells) in contact with the vascular system because reduced cell-to-cell cohesivity leads to reduced resistance to shear-induced release of endothelial cells from solid surfaces of these implants. This, in turn, leads to a dearth of human endothelial cells on grafts and biomedical devices post-implantation, which are subsequently colonized by other cell types, such as, for example, fibroblasts. Other cell types lack many of the growth properties characteristic of endothelial cells that are important for maintained functionality of the vasculature, so their growth leads to functional impairment of the implant, which can become so severe as to require replacement of the implant.

The present inventors have solved this longstanding problem by devising a method whereby endothelial cells (e.g., human endothelial cells) are altered to improve their ability to populate and adhere to the surface of a graft or biomedical device, particularly those in contact with the vasculature, wherein shear-stress induced cellular detachment is especially problematic. In brief, the present inventors have determined that increasing the amount of cadherin per cell and/or stabilizing cadherin association with the underlying cytoskeleton confer properties to the altered endothelial cells of the invention that improve their ability to populate and adhere to the surface of a graft or biomedical device. The novel and inventive aspects of the invention are underscored by an awareness that prior to the discovery of the present invention the field was targeted to methods directed to improving cellular attachment to the underlying graft material (cell-substratum adhesion), methods which largely proved ineffective. In contrast, the present

invention is focused on distinct methods directed to improving intercellular cohesion, which, in turn, improves the ability of cells to adhere to surfaces.

Objection to the Specification

The Examiner has indicated that the term "complete medium", as it appears in the specification, requires definition. Applicant asserts that the term "complete medium" is a standard term that is understood by ordinarily skilled practitioners. This is evidenced by performing a search of the electronic databases for the term "complete medium" either alone or in combination with either "definition" or "define" using a Google search engine. Print outs of three web sites identified by the above searches attest to this assertion and are attached hereto. Applicant, therefore, contends that an amendment to the specification to include a definition of the term "complete medium" is unnecessary because this is an art recognized term. In view of the above, the Examiner is respectfully requested to reconsider the objection to the specification and withdraw this objection.

Objection to the Claims

Claims 2-7, 10-15, and 24-27 are objected to for recitation of "A" rather than "The" at the beginning of each of these claims. Accordingly, claims 2-7, 10-15, and 24-27 are amended herein to recite "The" instead of "A". No issue of new matter is introduced by this amendment to the claims.

Claims 7-9, 11-15, 25, and 27 are objected to for the absence of a comma before the word "wherein". Accordingly, claims 7-9, 11-15, 25, and 27 are amended herein to include commas where suggested. No issue of new matter is introduced by this amendment to the claims.

Applicant has rendered these amendments to the claims in accordance with the Examiner's request. Thus, Applicant believes that the objections to the claims have been obviated.

Rejections under 35 USC § 112

Claims 24 and 27 are rejected under 35 USC § 112, second paragraph, for alleged indefiniteness. Claim 24 is amended herein to clarify aspects of the invention pertaining

to "native vascular endothelial cells". The term native is deleted by amendment presented herein. Specifically, the claim is amended to indicate that the method is directed to increasing the amount of cadherin per cell in vascular endothelial cells. Claim 27 is amended herein to elucidate what is meant by "functional molecules". In short, the term "functional molecules" is used to refer to those molecules capable of bridging cadherins to a cytoskeleton. The term "functional" is deleted from the claim as indicated herein since deletion of this term does not alter the meaning of the claim. Applicant, therefore, believes that the amendments to claims 24 and 27 are curative of the rejection based on alleged indefiniteness.

Rejections under 35 USC § 102

Claims 1-2, 4-6, 10, and 12-15 are rejected under 35 USC § 102(b) as allegedly anticipated by Schnittler et al. (American J. Physiology, 1997, 273:H2396-2405). In view of the amendments to the claims and Applicant's arguments herein below, the rejection, as it applied to claims 1-2, 4-6, 10, and 12-15, is respectfully traversed.

Instant claims 1-2, 4-6, 10, and 12-15 are directed to a method for populating a solid surface of a graft or biomedical device with cells comprising seeding a first population of altered endothelial cells onto said solid surface, wherein said altered endothelial cells exhibit increased cell-to-cell cohesion. The Schnittler et al. reference fails to provide any teaching relating to populating a surface of a graft or biomedical device with altered endothelial cells that exhibit increased cell-to-cell cohesion. Indeed, the Schnittler et al. reference is **silent** with respect to grafts and/or biomedical devices. Moreover, Schnittler et al. provide no commentary as to the challenges involved in populating a graft or biomedical device with endothelial cells, nor do they offer any solutions to such challenges. Thus, Applicant asserts that the Schnittler et al. reference fails to anticipate the method of the present invention as claimed in instant claims 1-2, 4-6, 10, and 12-15 and respectfully requests that the rejection of these claims under 35 USC § 102(b) be withdrawn.

Claims 1-7, 9-10, 12-15, and 23-27 are rejected under 35 USC § 102(b) as allegedly anticipated by Hordijk et al. (J. Cell Science, 1999, 112:1915-1923) with evidence provided by Stedman's Medical Dictionary (1995; Williams and Wilkins,

Baltimore). In view of the amendments to the claims and Applicant's arguments herein below, the rejection, as it applied to claims 1-7, 9-10, 12-15, and 23-27, is respectfully traversed.

Instant claims 1-7, 9-10, and 12-15 are directed to a method for populating a solid surface of a graft or biomedical device with cells comprising seeding a first population of altered endothelial cells onto said solid surface, wherein said altered endothelial cells exhibit increased cell-to-cell cohesion. The Hordijk et al. reference fails to present any guidance pertaining to populating a surface of a graft or biomedical device with altered endothelial cells that exhibit increased cell-to-cell cohesion. Instant claims 23-25 are directed to a method of increasing cell-to-cell cohesion in human vascular endothelial cells on a graft or biomedical device. The Hordijk et al. reference is also deficient with respect to teaching a method directed to increasing cell-to-cell cohesion in human vascular endothelial cells on a graft or biomedical device. In fact, Hordijk et al. are **mute** with respect to grafts and/or biomedical devices. Moreover, this reference fails to offer guidance regarding the challenges involved in populating a graft or biomedical device with endothelial cells and there is no appreciation indicated for the utility of increasing cell-to-cell cohesion of human vascular endothelial cells on a graft or biomedical device. Applicant further asserts that Stedman's Medical Dictionary fails to compensate for the deficiencies of the Hordijk et al. reference. In view of the above, Applicant asserts that the Hordijk et al. reference in view of Stedman's Medical Dictionary fails to anticipate the presently claimed methods of claims 1-7, 9-10, 12-15, and 23-27 and respectfully requests that the rejection of these claims under 35 USC § 102(b) be withdrawn.

Claims 1-5 and 10-11 are rejected under 35 USC § 102(b) as allegedly anticipated by Navarro et al. (J. Biol. Chem., 1995, 270:30965-30972). In view of the amendments to the claims and Applicant's arguments herein below, the rejection, as it applied to claims 1-5 and 10-11, is respectfully traversed.

Instant claims 1-5 and 10-11 are directed to a method for populating a solid surface of a graft or biomedical device with cells comprising seeding a first population of altered endothelial cells onto said solid surface, wherein said altered endothelial cells exhibit increased cell-to-cell cohesion. No teaching is provided in the Navarro et al. reference that addresses populating a surface of a graft or biomedical device with altered

endothelial cells that exhibit increased cell-to-cell cohesion. Moreover, Navarro et al. are **silent** with respect to grafts and/or biomedical devices. The authors offer no information relating to the challenges of endothelialization of a graft or biomedical device and thus, in turn, no solutions are purported to overcome such challenges. Thus, Applicant asserts that the Navarro et al. reference fails to anticipate the method of instant claims 1-5 and 10-11 and respectfully requests that the rejection of these claims under 35 USC § 102(b) be withdrawn.

In view of the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. §102 and withdraw the rejection.

Rejections under 35 USC § 103

Claims 1-15 and 23-27 are rejected under 35 USC § 103(a) as allegedly obvious over Schnittler et al. (*supra*), in view of Hordijk et al. (*supra*) with evidence provided by Stedman's Medical Dictionary (*supra*) and Navarro et al. (*supra*). In view of the amendments to the claims and Applicant's arguments herein below, the rejection, as it applied to claims 1-15 and 23-27, is respectfully traversed.

The deficiencies of these references with respect to alleged anticipation of the invention, as described above, are equally well applied to the rejection of the above claims on the basis of an alleged obviousness. To begin, none of these references even mentions grafts and/or biomedical devices. It therefore follows that a combination of these references also fails to provide commentary on grafts and/or biomedical devices. In view of the above, no combination of these references could reasonably be viewed as providing any guidance pertaining to a method for populating a solid surface of a graft or biomedical device with cells comprising seeding a first population of altered endothelial cells onto said solid surface, wherein said altered endothelial cells exhibit increased cell-to-cell cohesion. Nor could a combination of these references be construed properly as teaching a method directed to increasing cell-to-cell cohesion in human vascular endothelial cells on a graft or biomedical device. Thus, no motivation is provided that would lead an ordinarily skilled practitioner to combine the teaching of the Schnittler et al. reference with those of the Hordijk et al. reference, with evidence provided by

Stedman's Medical Dictionary, and/or the Navarro et al. reference to arrive at the presently claimed invention.

Moreover, certain passages of these references appear to teach away from the present invention. The Navarro et al. reference, for example, shows experimental evidence that truncated VE-cadherin can localize to intercellular contacts and promote homotypic aggregation. In a surprising result, these authors demonstrate that the truncated VE-cadherin is even more efficient in promoting calcium-dependent aggregation of transfectants than wild type VE cadherin. In that this truncated VE-cadherin lacks a cytoplasmic domain, which is required to interact with the underlying cytoskeleton, these findings argue against a significant contribution of stabilizing cadherin-cytoskeletal interactions to promote cadherin-mediated intercellular cohesion, which is an aspect of the present invention.

In view of the above, Applicant submits that the inventive aspects of the present method as recited in claims 1-15 and 23-27, and described in detail in the instant specification and summarized herein, are not obvious in view of the Schnittler et al. reference, the Hordijk et al. reference, Stedman's Medical Dictionary, or the Navarro et al. reference, when considered singly or in combination. Moreover, Applicant asserts that the Examiner has failed to present sufficient evidence to demonstrate a *prima facie* case of obviousness with respect to the instant claims. Accordingly, Applicant asserts that the rejection of claims 1-15 and 23-27 under 35 USC § 103(a) as allegedly unpatentable over the Schnittler et al. reference in view of Hordijk et al., Stedman's Medical Dictionary, and Navarro et al. is improper and respectfully requests that the rejection be withdrawn.

In view of the above arguments, the Examiner is respectfully requested to reconsider the validity of the rejection of the claims under 35 U.S.C. §103 and withdraw the rejection.

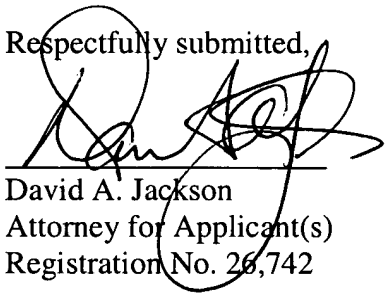
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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April 20, 2005

Enclosures: Petition for a Three-Month Extension of Time
Printed Copies of Three Web Sites Pertaining to a Definition for "Complete Medium"

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define:complete medium Search Advanced Search Preferences

Web

Definitions of **complete medium** on the Web:

- A culture medium that is enriched to contain all of the growth requirements of a strain of organisms. helios.bto.ed.ac.uk/bto/glossary/c2.htm

define:complete medium Search

Language Tools | Search Tips | Dissatisfied? Help us improve

Google Home - Advertising Programs - Business Solutions - About Google

Dictionary > C > *Complete Medium*

The ideal conditions for an organism to survive and grow.

complete medium

Definition:

SYN: enriched medium

A culture medium that is enriched to contain all of the growth requirements of a strain of organisms.

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